Remarks

The Office Action mailed 20 July 2007 has been received and reviewed. Claim 18 having been amended and claims 46-51 having been added, after entry of the amendment, the pending claims are claims 18-20, 23-26, 28-30, and 46-51. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim 18 is amended to recite that test compounds are selected for inclusion in the library based on having a solubility in deuterated water of at least about 1mM at room temperature and a molecular weight of no greater than about 350 grams/mole. Support for the amendment may be found at, for example, page 10, lines 7-10.

New claims 46-51 recite particular numbers of compounds in the library. Support for the new claims may be found at, for example, page 8, lines 19-23.

No new matter is introduced by these amendments.

Objection to the Specification

The Office Action objects to the specification as failing to provide proper antecedent basis for the claimed subject matter. Specifically, the Office Action asserts that the specification fails to recite the feature of claim 18 that reads, "wherein the ratio of target molecule to each test compound in each sample reservoir is about 1:1." Applicants respectfully disagree.

Support for the indicated language is found in original claim 27, now canceled. Additional support may be found at, for example, page 12, lines 23-24 and at page 13, lines 29-30. Because the language of claim 18 was present in Applicants' claims as originally filed and is otherwise described in Applicants' disclosure, Applicants respectfully submit that the specification, of which the claims are a part, provides proper antecedent basis for the language of claims 18. Applicants therefore respectfully request that the objection be withdrawn.

The 35 U.S.C. §103 Rejection

Claims 18-20, 23-26, and 28-30 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Hajduk et al. (*J. Am Chem Soc.*, 1997; 119:12257-12261) in view of Keifer (*Drugs of the Future*, 1998; *23*(3):301-317). Applicants respectfully traverse.

M.P.E.P. §706.02(j) states, "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." Applicants respectfully submit that the Office Action fails to establish a *prima facie* case of obviousness because, at least, the combination of Hajduk et al. and Keifer fails to teach or suggest all of the features recited in Applicants' claims.

Applicants have developed a method that involves the use of a relaxation-editing binding assay based on NMR spectroscopy that eliminates the need to develop a high-throughput functional assay, and also allows the method to be used on molecular targets lacking a known function.

One important element that contributes to the success of Applicants' method is selection of a suitable library of test compounds, which is neither taught nor suggested by the cited documents. Thus, claim 18 recites selecting a library comprising test compounds, wherein each test compound is selected based on having a solubility in deuterated water of at least about 1mM at room temperature and a molecular weight of no greater than about 350 grams/mole.

As stated in Applicants' specification at page 9, line 16, through page 11, line 3, for example:

> Important elements that contribute to the success of the methods of the invention preferably include developing a suitable small library of compounds to screen, carrying out the binding assay at low concentrations of target and near equimolar ratios of ligand

to target (for relaxation-editing), . . . and the capacity for rapid throughput of data collection. For example, for relaxation-editing NMR techniques, the concentration of target molecule is preferably no greater than about 1.0×10^{-4} M. . . .

The selection of compounds in a small library (preferably, at least about 75 compounds, more preferably, at least about 300 compounds, and most preferably, at least about 2000 compounds) is important in that its diversity should mimic the diversity of larger compound collections. Preferably, each component possesses many of the desirable qualities of a lead chemical template. These include water solubility, low molecular weight (preferably, no greater than about 350 grams/mole, more preferably, no greater than about 325 grams/mole, and most preferably, less than about 325 grams/mole), and amenability to synthetic chemistry elaboration. Templates possessing these qualities, as compared to a template selected randomly, are preferably considered to be predisposed to being lead-like and having an increased likelihood of ultimately leading to a drug.

Good structural diversity in a library increases the likelihood that one or more compounds will possess structural characteristics important for binding to a given molecular target. Predisposing the compounds to be water soluble, to have low molecular weight (preferably, no greater than about 350 grams/mole, more preferably, no greater than about 325 grams/mole, and most preferably, less than about 325 grams/mole), and to be amenable to synthetic elaboration increases the likelihood that a compound found to be a ligand will lead to a related compound or compounds suitable as a lead chemical template for use, for example, in a process of identifying an effective therapuetic and/or prophylactic agent. Additionally, the requirement for good water solubility (preferably, at least about 1.0×10^{-3} M in deuterated water at room temperature) is important in that it increases the likelihood of success of other downstream drug-design projects, such as co-crystallization attempts, calorimetry studies, and enzyme kinetic analyses.

Carrying out a relaxation-editing binding assay (preferably, a 1D ^{1}H NMR assay) at low concentrations of target (preferably, no greater than about 1.0×10^{-4} M, and more preferably, no greater than about 5.0×10^{-5} M) and near equimolar ratios of ligand to target creates the requirement that compounds testing positive for binding have affinities within a factor of about 3-4 of this same concentration (preferably, having a dissociation constant of no less than about 2.0×10^{-4} M). . . . This level of affinity is desired if the subsequent steps of focused screening and directed chemical elaboration are to be successful in elucidating a lead chemical template with very low affinity. . . . Carrying out the initial screening at these low concentrations also avoids detection of unwanted compounds with much smaller dissociation constants in the 1.0×10^{-3} M range, which are less specific in their binding and therefore harder to turn into lead chemical templates given their weak affinity initially.

The combination of Hajduk et al. and Keifer does not teach or suggest each and every aspect of Applicants' claimed invention. For example, this combination does not teach or suggest selecting a test compound for inclusion in the library based on its solubility and molecular weight. Hajduk et al. is said to teach "detection of ligand binding to mixtures comprising a library of nine compounds" wherein the "compounds read on the test compounds having molecular weights no greater than about 350 grams/mole" and "solubility in deuterated water of at lest about 1 mM at room temperature[.]" (Office Action mailed July 20, 2007, p. 4, lines 2, 5-6, and 18-19). Hajduk et al. fail to teach or suggest selecting test compounds *based on* the combination of their solubility and molecular weight in order to form a library that includes test compounds that have a molecular weight no greater than about 350 grams/mole and a solubility in deuterated water of at lest about 1 mM at room temperature. This is in part due to the different objectives of Hajduk et al. and Applicants' method. Hajduk et al. analyzed, for each of two macromolecules, one compound known to be a ligand of the macromolecule and eight compounds known not to bind the target macromolecule in order to demonstrate the utility of NMR methods for detecting compounds that bind to a macromolecule. The *only* characteristic Hajduk et al. considered when selecting test compounds was whether they were known to bind particular macromolecules.

In contrast, Applicants' claimed method is used to screen test compounds to determine *whether* a test compound binds to a specified target. In order to screen test compounds efficiently, Applicants have determined that selecting test compounds based on their solubility and molecular weight so that the library includes test compounds having the recited solubility and molecular weight improves the chances of finding a ligand of the specified macromolecule that can ultimately be used as a drug template. Applicants describe the importance of selecting test compounds in this way as follows, "Templates possessing these qualities, as compared to a template selected randomly, are preferably considered to be predisposed to being lead-like and having an increased likelihood of ultimately leading to a drug." (Specification, page 10, lines 1-4). Hajduk et al. were concerned only with demonstrating that ligand-macromolecule binding

could be detected. Thus, they had no motivation to consider or develop ways to improve the efficiency of their method when practically applied to screening up to 1000-fold more test compounds whose binding characteristics with respect to the target macromolecule were unknown prior to the analysis. Applicants' method includes selecting test compounds *based on* certain characteristics–solubility and molecular weight–that contribute to the efficiency of Applicants' methods and represents an advance that is neither taught nor suggested by Hajduk et al.

Applicants' claims recite a method that includes expressly, intentionally, and consciously selecting test compounds that have a solubility in deuterated water of at least about 1mM at room temperature and a molecular weight of no greater than about 350 grams/mole, as opposed to the teaching of Hajduk et al.: merely selecting eight compounds that were known to not bind a specified macromolecule. Applicants' methods include the conscious selection of test compounds to be included in the library *based on* the combination of their solubility and molecular weight. Thus, the present claims recite a *cognitive and discretionary* step that was untaught and not suggested prior to Applicants' disclosure. Applicants have discovered that by making this cognitive and discretionary selection of test compounds, one can improve the chances that a compound identified as a ligand of the specified macromolecule has certain characteristics that may be desirable for a compound serving as a lead for developing a new drug product. It is this cognitive and discretionary selection of test compounds to be included in the library that is missing from Hajduk et al.

Nothing in Keifer, either alone or in combination with Hajduk et al., teaches or suggests selecting compounds for a compound library based on the compounds having a molecular weight no greater than about 350 grams/mole and a solubility in deuterated water of at lest about 1 mM at room temperature. Thus, the combination of Hajduk et al. and Keifer fails to teach or suggest selecting compounds for a compound library based on the compounds having a molecular weight no greater than about 350 grams/mole and a solubility in deuterated water of at lest about 1 mM at room temperature.

Because the combination of Hajduk et al. and Keifer fails to teach or suggest all of the features recited in Applicants' claims, the combination of Hajduk et al. and Keifer fails to establish a *prima facie* case of obviousness against claims 18-20, 23-26, and 28-30. Thus, Applicants respectfully submit that claims 18-20, 23-26, and 28-30 are patentable under 35 U.S.C. §103(a) over the combination of Hajduk et al. and Keifer and request that the rejection be withdrawn.

New Claims

New claims 46-51 recite specific numbers of compounds in the compound library to be screened for binding to a specified macromolecule. New independent claim 49 is patentable because prior to Applicants' disclosure, there was no teaching or suggestion of a method of identifying a compound that binds to a target molecule in which the method includes selecting a library comprising at least 75 and no more than about 10,000 test compounds, wherein each test compound has a solubility in deuterated water of at least about 1 mM at room temperature and has a molecular weight of no greater than about 350 grams/mole. Claims 50 and 51 depend from claim 49 and are, therefore, patentable for at least all of the reasons that claim 49 is patentable.

Each of claims 46-48 depends, directly or indirectly, from claim 18 and, therefore, also includes all of the features recited in claim 18. Thus, claims 46-48 are patentable for at least all of the reasons that claim 18 is patentable.

Amendment and Response
Serial No.:10/694,385
Confirmation No.: 5758
Filed: 27 October 2003
For: METHODS FOR CREATING A COMPOUND LIBRARY AND IDENTIFYING LEAD CHEMICAL TEMPLATES AND LIGANDS FOR TARGET MOLECULES

Summary

It is respectfully submitted that the pending claims 18-20, 23-26, 28-30, and 46-51 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted
By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

October 22, 2007
Date

By: Ann M. Mueting
Ann M. Mueting
Reg. No. 33,977
Direct Dial (612) 305-1217

CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to **Mail Stop Amendment**, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 22nd day of October, 2007, at 4:07 pm (Central Time).

By: Dani Mayo
Name: Dani Mayo